

Seminar

Dipanjan CHOWDHURY, Ph. D.,

Chief of the Division of Radiation and Genome Stability, Dana-Farber Cancer Institute

Professor, Harvard Medical School



Monday, January 13th 2020

11:30 am

Centre de recherche - Orsay Nelly Riguet du Bâtiment 111

«New Factors in DNA Double Strand Break Repair: Impact on cancer therapy»

The Dipanjan Chowdhury Lab investigates how human cells sense and repair DNA damage. Loss of genome integrity due to DNA damage has long been established as a critical contributor to cancer and tumorigenesis.

Our work therefore focuses on how cells maintain genome integrity. Through genetic, biochemical, and proteomic approaches, as well as collaboration with structural biologists, computational biologists and mouse geneticists, we aim to achieve better understanding in cancer etiology and the development of effective cancer diagnoses and therapies. Whether it is searching for potential treatments to radiation exposure, or the causes and treatment of ovarian cancer, we strive for research that makes a positive impact. Damage to DNA is induced daily from metabolites and occurs upon exposure to ionizing radiation. One type of DNA damage, double-strand DNA breaks (DSBs), is particularly toxic to cells—a single DSB is enough to cause cellular lethality if left unrepaired. Cells have evolved factors that act in two major mechanistically distinct pathways to repair DSBs. One pathway uses the sister chromatid available during S phase as template to synthesize DNA to replace the damage, termed homologous recombination (HR). Another pathway, termed non-homologous end joining (NHEJ), molecularly joins the two ends of the DNA break during G1, when sister chromatid is not available. The relative contribution of these two competing pathways differ in different cell types and in different phases of the cell cycle. The balance of pathway choices between these two pathways is therefore critical for maintaining genomic stability. Two key DNA repair molecules, 53BP1 and BRCA1, compete to facilitate NHEJ and HR, respectively. A decisive factor in the choice between DSB repair pathways is in the competition between DNA end protection that is necessary for NHEJ, and DNA end resection that is necessary for HR. DSB end resection that facilitates HR pathway must be appropriately restricted to S/G2 phases of the cell cycle, when the intact sister chromatid is available. Depletion of NHEJ promoting factors such as 53BP1 allows DNA end resection in the G1 phase, thereby impairing DSB repair and causing genomic instability. Conversely, loss of the HR protein, BRCA1 (critical for initiating end resection) allows the error-prone NHEJ pathway to dominate throughout the cell cycle potentially also contributing to mutations/deletions. Inhibitors of the DNA repair protein poly ADP-ribose polymerase (PARP) have been an effective therapy for cancer patients with BRCA1-deficiency, since PARP inhibition induces DSB that requires BRCA1-mediated HR to repair the damage. However, over time these cancers acquire resistance to PARP inhibitor, by losing 53BP1 or pro-NHEJ associated factors (RIF1, PTIP) that consequently restore resection and the activation of HR pathway. Our aim is to identify and understand biomolecules that modulate the activities of 53BP1 and BRCA1, thereby influencing the cellular choice between HR and NHEJ repair pathway under various physiological conditions.

Invited by:

*Sarah Lambert
Stephan Vagner*

Unité « Genome integrity, RNA and Cancer ».

Contact(s):

Sarah.Lambert@curie.fr
Stephan.Vagner@curie.fr